REMARKS

I. Status of Claims

Claims 1-7, 9, 11 and 14 are pending in this application. Claim 14 is currently withdrawn. Claims 1-7, 9 and 11 have been rejected. Applicants note that the rejection of claims 1-3, 5-7, 9 and 11 under 35 U.S.C. § 102(a) and (e) have been withdrawn.

II. Rejection under 35 U.S.C. § 112, second paragraph, indefiniteness

Claims 1-4 and 11 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that it is not clear what the phrase "a mutant *Neisseria meningitides* ADP-ribosylating enzyme" means in the context of the claims nor is it clear what "biological or structural or chemical or functional elements/features" must be encompassed by the phrase. Applicants disagree and respectfully traverse the rejection and its supporting remarks. The claim distinctly points out and claims a mutant *Neisseria meningitides* ADP-ribosylating enzyme with a substitution at one or more of amino acids Glu-109, Glu-111 or Glu-120. The structure claimed is clear – any *Neisseria meningitides* ADP-ribosylating enzyme that has an amino acid substitution at one or more of the three residues specified. By virtue of having one or more of the claimed amino acid substitutions, the enzyme would be characterized as a mutant.

One of skill in the art would clearly understand the meets and bounds of what "structural or chemical or functional elements/features" are encompassed by the term "*Neisseria meningitides* ADP-ribosylating enzyme". ADP-ribosylating enzymes are a well documented class of bacterial toxins that, despite lacking primary sequence homology, exhibit a highly conserved catalytic domain that serves as the NAD-binding cavity and acts as a unique molecular signature for this class of enzymes. Due to the extensive characterization of this class of enzymes over the past three decades, those of skill would appreciate the scope of term *Neisseria meningitides* ADP-ribosylating

enzyme and would not need the specific sequence to identify the enzyme to identify it as such. By way of example, one of skill in the art does not need sequence information to understand what is meant by an ADP-ribosylating enzyme discussed in a peer-reviewed journal article or academic text as the defining characteristics are inherent in the enzyme classification. Numerous such articles have been submitted in prior IDSs. The peer-reviewed journal articles use the term ADP-ribosylating enzymes without necessarily specifying any sequences and those of skill in the art have no difficulty in understanding what is being discussed in the papers. The enzyme name alone is enough to encompass the structural, chemical and functional properties of the enzyme as these are the exact properties that classify it as an ADP-ribosylating enzyme.

The Examiner also questions how many changes to SEQ ID NO: 1 can be present and still be a mutant *Neisseria meningitides* ADP-ribosylating enzyme. This question is not relevant to the pending claims since the claims specify the nature of the mutation which is substitution at one of the three recited residues. If one of skill in the art desires to include additional mutations, one of skill in the art is free to introduce such mutations. Thus, the presence or absence of other mutations do not affect whether the enzyme is within the scope of the claims. All that is required by the claims is whether there is a substitution at one of the three specified amino acid residues. The skilled artisan would never make any and every mutation possible as there is clear direction available in the art as to what constitutes a "mutant" form of the enzyme. If a *Neisseria meningitides* ADP-ribosylating protein has a substitution at one or more of the three amino acid positions recited, it is a mutant *Neisseria meningitides* ADP-ribosylating protein within the scope of the claims. Moreover, there is ample guidance in the literature to aid one of skill in the art in making a mutant *Neisseria meningitides* ADP-ribosylating protein enzyme.

Applicants therefore respectfully request the Examiner withdraw the rejection of claims 1-4 and 11 under 35 U.S.C. § 112, second paragraph.

III. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not reasonably providing enablement for any mutant *Neisseria meningitides* ADP-ribosylating protein or fragments thereof with any substitution at Glu-109 or Glu-111 or Glu-120.

Applicants respectfully traverse the rejection and its supporting remarks. Applicants agree with the Examiner that the specification covers and is enabling for an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 2, 3 or 4 having reduced or eliminated ADP-ribosylating activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). However, the Examiner alleges that because the claimed invention is open-ended and would cover other mutations in the enzyme outside of the substitution mutations, the Applicants have to enable one of skill in the art to make and use all of these other mutations in addition to enabling one of skill in the art to make and use the claimed substitution mutations.

As stated above, such other mutations are irrelevant to the scope of the claims since their presences or absence does not affect whether the enzyme is within the scope of the claims – all that matters is whether there is a substitution at one of the three specified residues. The Examiner is improperly requiring the Applicants to show, *a priori*, that every species disclosed in the specification is operable. This is not the proper test of enablement. The analysis is whether undue experimentation would be required. Undue experimentation is clearly not required. Applicants have shown that even the most mild of substitutions at the Glu-109, Glu-111 or Glu-120 are sufficient to inactivate the toxic activity therefore one of skill in the art would appreciate that any *Neisseria meningitides* ADP-ribosylating mutant with a substitution at Glu-109, Glu-111, or Glu-120 would inactivate the toxic activity without needing to actually test such other substitution mutants. Finally, as long as the *Neisseria meningitides* ADP-ribosylating mutant has such a substitution meeting the claim limitation, the mutant will not have toxic activity regardless of any other additional mutations generated elsewhere in the enzyme.

Additionally, the claims are not drawn to any and all *Neisseria meningitides* ADP-ribosylating mutant proteins that function for any purpose but rather require that the mutant protein have a substitution at one or more of amino acids Glu-109 or Glu-111 or Glu-120 which are well known in the art to be the catalytic residues. The claimed mutations can be introduced into any other context and will function as intended, i.e., the mutant enzyme will show reduced toxic activity with the substitution mutation in at least one of the three specified residues.

Further, the specification must be viewed in light of information known in the art. The M.P.E.P. § 2164.01 states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure ***coupled with information known in the art*** (citing *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989)). The Office must consider evidence provided by the Applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. The evidence provided by the Applicant need not be conclusive but merely convincing to one skilled in the art (PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster*, 185 USPQ 152 (CCPA 1975); and *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

The structure and function of ADP-ribosylating enzymes has been well established in the art for over 20 years, with an abundance of work focusing on the characterization of the catalytic residues responsible for the ADP-ribosylating activity. This catalytic activity is essential for understanding the mechanism of toxin pathogenesis. More importantly, these toxins are potent immune stimulators. To be useful as immune stimulators, the catalytic activity must be reduced or eliminated so that the polypeptides are not toxic. Thus, a great deal has been published about the function, i.e., the catalytic activity, how to inactivate that catalytic activity, and how that relates to the structure of the polypeptides.

The first x-ray crystal structure of a bacterial toxin, specifically exotoxin A from *Pseudomonas aeruginosa,* was published in 1986 by Allured and Collier (PNAS 1986). By 1991, fifteen years before the filing date of the current application, over 40 ADP-ribosylating enzyme

structures had been determined, contributing a plethora of structural data that allowed the essential catalytic residues to be mapped (Rappuoli & Pizza 1991, The Comprehensive Sourcebook of Bacterial Protein Toxins, Third Edition, Chapter 1, p. 12). The studies disclosed herein illustrate a strong correlation between mutations in the predicted catalytic residues of SEQ ID NO: 1 and reduced ADP-ribosylating activity (see Figure 4). Taken together, one of skill in the art could readily identify mutants that would exhibit reduced or eliminated ADP-ribosylating activity based on the key catalytic residues that are present or absent in the polypeptide structure.

In addition to the general catalytic residues known to be important for catalytic activity, structure-function analysis of ADP-ribosylating enzymes over the past three decades has identified an "extremely conserved" glutamate positioned in the catalytic region that is "essential" for catalytic activity (Carroll and Collier, 1984; Barbieri et al. 1989; Antoine et al. 1993; Thanabalu et al. 1991; Tsuji et al. 1991). This residue maintains the exact same atomic coordinates in all available ADP-ribosylating structures and has been demonstrated to be essential for catalysis in most toxins (Tweten et al. 1985; Douglas and Collier 1987; Burnette et al. 1988; Pizza et al. 1988; Wilson et al. 1990; Douglas and Collier 1990; Lobet et al 1991). Biochemical, structural and genetic data confirmed this absolute requirement for the enzyme activity (Domenighini 1994). The Applicants' own sequence alignment analysis and mutant enzyme activity data suggests this critical residue corresponds to Glu-120 in the *Neisseria meningitides* ADP-ribosylating enzyme. Based on Applicants' alignment data and on the overwhelming structural homology evidence in the literature, it would be clear to one of skill in the art that a mutation in this residue would impair the function of an ADP-ribosylating enzyme.

The present record establishes that one of skill in the art could practice the claimed invention without undue experimentation. The specification is replete with representative examples and provides sufficient guidance to enable a *Neisseria meningitides* ADP-ribosylating enzyme with one or more substitutions at Glu-109 or Glu-111 or Glu-120. So long as it is clear that some species render a composition operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1, of 35 U.S.C. §112 (*In re Cook*, 439 F.2d 730, 735, 169

USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir.1988). However, in this context, to be inoperative would somehow require that the mutations outside the three core catalytic residues restore activity of the toxin despite lacking the catalytic core. Moreover, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof (*In re Angstadt* at 504; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29, 32, CCPA 1976.)

Applicants note that on page 11, lines 5-7, of the Office Action dated Nov. 7, 2008, the Examiner incorrectly recites and characterizes a statement by the Applicant. The Examiner quotes the Applicant as stating:

> *"It is highly unlikely if not impossible that one of skill in the art could be working on an enzyme with other mutations where introduction of the claimed mutations would lead to an enzyme with reduced activity"*

In fact, the original language recited the ***opposite***, stating "it is highly unlikely if not impossible that one of skill in the art could be working on an enzyme with other mutations where introduction of the claimed mutations would ***not*** lead to an enzyme with reduced activity." (For reference, the Examiner correctly recited the statement on page 8 paragraph B lines 15-17 of the above referenced Office Action when quoting the Applicants' previous arguments.) The original language is in agreement with the statement by the Examiner on page 6, lines 7-9 in the Office Action, which states that one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions. It is therefore entirely predictable that the accumulation of amino acid substitutions would lead to a reduction in enzyme function. Thus, it is highly improbable that one of skill in the art could introduce the claimed mutations into any ADP-ribosylating enzyme without there being a reduction in enzyme activity.

Applicants submit that there is ample guidance provided in the specification and that undue experimentation is not required to practice the claimed invention because the claims are enabled

throughout their scope. The specification as filed clearly teaches mutant *Neisseria meningitides* ADP-ribosylating enzymes with one or more substitutions at Glu-109 or Glu-111 or Glu-120 which are well known in the art to be important residues for catalytic activity. Further, the Examiner did not in any way establish unpredictability. As such, the enablement requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9 and 11 under U.S.C. §112, first paragraph, enablement.

IV. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has not established a *prima facie* case of failure to comply with the written description requirement. The specification must be taken as complying with the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). As such, the Examiner has not provided any reason to doubt that the specification fails to provide an adequate written description of the presently claimed invention.

The ultimate question that must be asked is whether one of skill in the art would recognize that the inventors were in possession of the claimed invention as of filing the patent application. In the present application, the claimed invention is to a mutant *Neisseria meningitidis* ADP-ribosylating enzyme with a substitution at one of three exactly specified locations in the enzyme. Those three locations are known to be the three catalytic residues from homology to other ADP-ribosylating enzymes and the mutational experiments set forth in the specification. As describe in detail above, the structure and function of ADP-ribosylating toxins have been well established in the art for over 20 years, with a substantial amount of work focusing on the characterization of the

catalytic residues responsible for the ADP-ribosylating activity. It is clear that at the time of filing, one of skill in the art would, based upon the teachings in the specification of the *Neisserial* variant and in light of the vast body of knowledge regarding homologous ADP-riboslyating toxins from *e. coli* and *Cholera*, have immediately recognized that the recited catalytic residues contribute to ADP-ribosylating activity and that any of the claimed substitutions would lead to a reduction in enzyme activity. Thus, it is unquestionable that Applicants have met the written description requirement as they have demonstrated to one of skill in the art that they were in possession of the claimed invention and that they have broad coverage rather than merely a single amino acid sequence.

Further, the Examiner has remained silent on the two recent cases from the Federal Circuit, *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006) and *Capon v. Eshhar*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005), which are summarized in the MPEP in section 2163(a)(1), that the Applicants have cited in previous office actions. Both of these cases make clear that the case cited by the Examiner, *Eli Lilly*, only applies to new genes in entirely new functional classes. The present invention, however, is directed to specific mutations at one of three exactly specified residues in a protein that is in a well characterized class much like the case in *Capon* where the inventors were claiming mutations that inactivated certain functions in viral proteins (without even specifying the exact residues to be mutated which makes the presently claimed invention more specific than that claimed in *Capon*). Furthermore, in *Capon*, the inventors did not disclose the sequence of even a single protein from the class of viruses in which the mutations were claimed.

Applicants respectfully request that the Examiner respond and explain his reasoning for maintaining the rejection in view of the preceding arguments.

The Examiner's assertion that the fact that the claims are not limited to mutants that have mutations at only the three specified residues is irrelevant to determining the scope of the written description requirement. To satisfy the written description requirement, one must convey that the inventors were in possession of ***that which is claimed***. The Examiner is asserting that the Applicants have not satisfied the written description requirement because of a failure to disclose

elements that are not actually claimed but could be covered by virtue of the claims being open-ended comprising claims. The Examiner is correct that the claims, because they are open-ended, would cover mutant enzymes that have other mutations in addition to a substitution mutation at one of the three residues as claimed. However, these other mutations are not claim elements required for one to meet the claims. As long as the inventors have described ***their*** invention sufficient to show possession of the ***claimed*** invention, it is irrelevant whether they have described every other thing that could be combined with their invention. Thus, Applicants have met the written description requirement as they have demonstrated to one of skill in the art that they were in possession of the claimed invention.

As the Office Action makes a general allegation of unpredictability, Applicants respectfully submit that the Examiner has failed to provide any reasons to doubt that one of ordinary skill would recognize that Applicants had possession of the invention at the time of filing of the application and has therefore failed to make a *prima facie* case for lack of written description. Any allegation of unpredictability in the art generally is inapplicable as the situation for ADP-ribosylating toxins is well developed. Therefore if the Examiner wishes to assert that there is unpredictability with regard to the claims, Applicants respectfully request that the Examiner cite relevant art for this proposition, i.e., art that teaches that ADP-ribosylating toxins were unpredictable. Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9 and 11 under U.S.C. §112, first paragraph, written description.

V. Double Patenting

The Examiner has provisionally rejected claims 1-7, 9 and 11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 28, 36, 38, 45 and 46 of Masignani et al., (US Application No.: 10/472,681).

Applicants remind the Examiner that claims and not preferred embodiments must be used to make a rejection. In addition, it is not sufficient that the claims overlap, the claims in this application must be anticipated by (i.e., the claims in the other patent application must be entirely

within the scope of a claim in this application), or obvious in light of the claims in the other application. However, Applicants respectfully request that the examiner hold this rejection in abeyance until such time as there is an indication of otherwise allowable subject matter. Only at that time will the Applicants be able to determine whether an obviousness-type double patenting rejection is applicable and at such time Applicants may amend 10/472,681 to remove such claims if necessary.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. **223002103000**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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